REMARKS

This paper is in response to the non-final Office Action dated June 16, 2004. Applicants respectfully assert that this Reply is fully responsive to each of the objections raised in the outstanding Office Action.

Claims 1-19 were pending in the instant application. Claim 10 has been canceled without prejudice to Applicants' right to pursue the canceled subject matter in other applications. Claims 1, 2, 6-9, 11, 13, 18 and 19 have been amended. The amended claims are fully supported by the originally filed claims and the specification. As such, no new matter has been added.

Claim 19 is objected to because of informalities. Applicants have corrected such informalities by amendment herein. Accordingly, Applicants believe that this objection has been obviated.

Claim 8 is rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite due to use of the terms "adrenaline" and "L-epinephrine" in the Markush group. Applicants have corrected the Markush group by amendment herein. As such, Applicants respectfully request that the rejections under 35 U.S.C. § 112, second paragraph, be withdrawn.

THE CLAIMS ARE NOT ANTICIPATED BY SWOPE

Claims 1-3, 6, 8-9, 11-12, 16 and 19 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Swope et al., 1995, Experimental Cell Research 217:453-459 (hereinafter "Swope").

The Office Action alleges that Swope teaches a modified growth culture medium comprising MCDB153, fetal bovine serum, insulin, transferrin, alpha-tocopherol, fibroblast

growth factor, penicillin-streptomycin, α–melanocyte stimulating hormone and endothelin-1. Office Action at page 3. Applicants respectfully point out that Swope fails to teach each and every limitation of the claims as amended. In particular, the amended claims require that the composition have at least epinephrine as a natural, physiological cAMP-elevating agent. Swope does not disclose epinephrine in its culture media.

Accordingly, Applicants submit that the presently claimed compositions for culturing epidermal melanocytes, and methods of using the same, are clearly distinct from the compositions and methods of Swope. As such, Swope cannot anticipate the claimed invention, and Applicants respectfully request that the rejections under 35 U.S.C. § 102(b) in view of Swope be withdrawn.

THE CLAIMS ARE NOT ANTICIPATED BY YANASE

Claims 1-6, 8 and 10 are rejected under 35 U.S.C. § 102(b) as allegedly being unpatentable over U.S. Patent No. 5,916,809 to Yanase et al., 1994 (hereinafter "Yanase").

The Office Action alleges that Yanase discloses a medium for culturing normal human epidermal melanocytes, in which the medium comprises a basal medium, one or more growth factors useful for growth of human melanocytes, serum, antibiotics, and bovine pituitary extract containing α–melanocyte stimulating hormone. Office Action at page 4. Applicants respectfully point out, however, that Yanase fails to teach each and every limitation of the claims as amended. In particular, the amended claims require that the composition contain at least epinephrine as one of the natural, physiological cAMP-elevating agents. Yanase does not disclose the use of epinephrine in its culture media.

Accordingly, Applicants submit that the presently claimed compositions for culturing epidermal melanocytes are clearly distinct from the culture media of Yanase. As such, Yanase cannot anticipate the claimed invention, and Applicants respectfully request that the rejections under 35 U.S.C. § 102(b) in view of Yanase be withdrawn.

THE CLAIMS ARE NOT ANTICIPATED BY HU

Claims 1-6 are rejected under 35 U.S.C. § 102(b) as allegedly being unpatentable over Hu et al., 2000, Exp. Eye Res. 71:217-224 (hereinafter "HuI").

Specifically, the Office Action alleges that HuI anticipates the claimed invention because it "teach[es] the preparation of a melanocyte culture medium comprising the addition of cAMP-elevating isoproterenol into a complete FIC medium containing F12 basal medium supplemented with 10% FBS, glutamine, bFGF, IBMX, cholera toxin and gentamycin." Office Action at page 5. Applicants respectfully disagree. Applicants respectfully point out that isoproterenol is a synthetic beta-adrenergic agonist, and thus does not meet the claim element of a natural, physiological cAMP-elevating agent as required by the present invention.

Nevertheless, HuI fails to teach each and every limitation of the pending claims. In particular, the rejected claims (as amended herein) require that the composition contain at least hepatocyte growth factor as one of the growth factors. HuI does not disclose the use of hepatocyte growth factor in its culture media.

Accordingly, Applicants submit that the presently claimed compositions for culturing epidermal melanocytes are clearly distinct from the culture medium taught by HuI. As

such, Hul cannot anticipate the claimed invention, and Applicants respectfully request that the rejections under 35 U.S.C. § 102(b) in view of Hul be withdrawn.

THE CLAIMS ARE NOT OBVIOUS IN VIEW OF CHEN AND SWOPE

Claims 1-6, 8-9 and 11-19 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Chen et al, 2000, J. Dermatology 27:434-439 (hereinafter "Chen") in view of Swope.

Applicants note with appreciation that Claim 7 (which requires hepatocyte growth factor) and Claim 10 (which requires epinephrine) are not deemed to be unpatentable pursuant to 35 U.S.C. § 103(a) in view of Chen and Swope. Applicants have amended the claims such that all the claims require a composition comprising hepatocyte growth factor and epinephrine.

The Office Action alleges that "it would have been obvious for an ordinary skilled artisan to modify the method taught by Chen et al. by utilizing a modified melanocyte culture medium disclosed by Swope et al. to expand autologous melanocytes prior to transplanting them into patients with segmental vitiligo due to the advantages offered by the modified melanocyte culture medium of Swope et al." Office Action at page 8. Applicants respectfully disagree.

"To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art." MPEP 2143.03. Even if combined as proposed by the Office Action, each and every limitation of the amended claims cannot be met by Chen and Swope since neither reference teaches compositions comprising hepatocyte growth factor and epinephrine. Accordingly, Applicants respectfully submit that neither Chen nor Swope, singly or taken together, teach or suggest the presently claimed invention.

As such, Applicants respectfully request that the rejections under 35 U.S.C. § 103(a) in view of the combination of Chen and Swope be withdrawn.

THE CLAIMS ARE NOT OBVIOUS IN VIEW OF CHEN, SWOPE AND HU

Claims 1, 8 and 10 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Chen in view of Swope and further in view of HuI.

As indicated above, neither Chen nor Swope teaches compositions comprising hepatocyte growth factor and epinephrine. The Examiner acknowledges that "none of the references teach the use of L-epinephrine as a natural physiological cAMP-elevating agent." Office Action at page 9. Nevertheless, the teachings of HuI are proffered to meet the claim element missing from the combination of Chen and Swope. However, the rejected claims (as amended herein) require a composition that also contains at least hepatocyte growth factor as one of the growth factors. HuI does not disclose the use of hepatocyte growth factor in its culture media. Therefore, even if Chen, Swope and HuI are combined as proposed by the Office Action, each and every limitation of the amended claims are not met and cannot make obvious the presently claimed invention.

Applicants also disagree with the assertion that "it would have been obvious for an ordinary skilled artisan to include c-AMP elevating agents such as epinephrine, isoproterenol, salbutamol and metaproterenol taught by HuI et al. in the melanocyte culture medium of the combined teachings of Chen et al. and Swope et al. because they are already demonstrated to be useful for [uveal] melanocyte growth and melanogenesis." Office Action at page 9. HuI relates to uveal melanocytes which are entirely different cells (of the eye), and have a distinct pathophysiology when compared to the epidermal melanocytes of the skin.

As set forth in the accompanying Declaration of Dr. Dan-Ning Hu ("Rule 132 Declaration"), one of ordinary skill in the art would understand that uveal melanocytes are so different from epidermal melanocytes ("EM") that there would be no reasonable expectation of success of using a culture medium - shown to be useful for uveal melanocyte growth and melanogenesis - for growing EM suitable for transplantation (*i.e.*, EM exhibiting proliferative growth, melanin production and migratory behavior).

EM differ from uveal melanocytes in at least the following respects. EM respond to ultraviolet light by increasing melanogenesis whereas uveal melanocytes do not (1, 2, 3). EM transfer melanin to keratinocytes whereas uveal melanocytes do not transfer melanin (1, 2, 3). EM respond to many inflammatory diseases by changing of skin color but this is very rare in the eye (1, 2). Whereas the malignant transformation of EM (i.e., cutaneous melanoma) is strongly correlated with an increased UV exposure over years, uveal melanoma has no such correlation (4,5). The metastasis of transformed EM occurs mainly through the lymphatics such that skin metastasis is common. In contrast, the metastasis of transformed uveal melanocytes is mainly through the blood vasculature, ultimately lodging in the liver (6). Cytogenetics studies indicate mutational hotspots on chromosomes 1, 6, 7, 9 and 10 of transformed EM as opposed to chromosomes 3, 6 and 8 of transformed uveal melanocytes (6, 7).

RAS and BRAF mutations are the most common mutations in transformed EM, and ß-catenin is mutated in 25% of transformed EM. There are no such RAS, BRAF or ß-catenin mutations in the pathogenesis of uveal melanocytes (6, 8). In transformed EM, α2 integrin is common and α5 integrin is rare. In direct contrast, α2 integrin is rare and α5 integrin

is common in transformed uveal melanocytes (9). EM respond to both ACTH and α-MSH *in vitro* whereas transformed respond to neither (1).

In addition, uveal melanocytes respond to β2 (but not β1) adrenoreceptor agonists (10), quite unlike EM which respond to both β1 and β2 adrenoreceptor agonists. Therefore, one of ordinary skill in the art would have been led, if at all, to use a specific β2 adrenoreceptor agonist (e.g., for cultures of uveal melanocytes). Notably, the person of ordinary skill in the art would have had no motivation (in fact, would have been disinclined) to use the non-specific agonist, epinephrine, for culturing uveal melanocytes where specific β2 adrenoreceptor agonists were readily known and available.

As a result, the effect of any compound useful for culturing uveal melanocytes would necessarily be tested separately on EM for its suitability. Even if a person of ordinary skill in the art may have been motivated to empirically test every adrenoreceptor agonist in EM cultures, that is not the proper standard for obviousness; instead the standard is whether a person of ordinary skill in the art at the time of filing would have had a reasonable expectation of success using claimed invention. *See e.g., In re Antonie*, 559 F.2d 618, 620 (C.C.P.A. 1977) (obvious to try is not the standard of 35 U.S.C. § 103(b)); *In re Merck & Co., Inc.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986) ("[T]he board's decision was premised on an impermissible obvious to try standard."). As explained in the enclosed Rule 132 Declaration, Applicants assert that there was no reasonable expectation of success of using epinephrine to culture EM at the time of the present invention.

Accordingly, Applicants respectfully submit that neither Chen, Swope nor Hul, taken singly or in combination, teach or suggest the presently claimed invention. As such,

Applicants respectfully request that the rejections under 35 U.S.C. § 103(a) in view of the combination of Chen, Swope and HuI be withdrawn.

THE CLAIMS ARE NOT OBVIOUS IN VIEW OF YANASE, SWOPE AND HU

Claims 1, 6 and 7 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Yanase, Swope and Hu, 2000, Pigment Cell Res. 13 Suppl. 8:81-86 (hereinafter "HuII").

The Office Action states that Yanase discloses a medium for culturing normal human epidermal melanocytes. That medium comprises a basal medium, one or more growth factors useful for growth of human melanocytes, serum, bovine pituitary extract, and antibiotics. Office Action at page 11. The teachings of HuII are proposed to be combined with those of Yanase to meet the presently claimed invention.

First, Yanase does not teach or suggest a culture media containing epinephrine, as required by the claims as amended. Second, as acknowledged by the Examiner (Office Action at page 11), Yanase does not teach having, as a constituent of the culture medium, hepatocyte growth factor which is also required by the claims as amended. Nevertheless, the Office Action states that "it would have been obvious for an ordinary skilled artisan to include hepatocyte growth factor in the culture medium taught by Yanase et al. because HGF has been shown to stimulate melanogenesis and/or growth of human [uveal] melanocytes *in vitro* by Hu." Office Action at page 11. Applicants respectfully disagree.

Importantly, HuII also relates only to uveal melanocytes which, as discussed above and presented in the enclosed Rule 132 Declaration, are entirely different from EM. As

stated above, EM are biologically dissimilar to uveal melanocytes in many respects including differing by their response to ultraviolet light (1, 2, 3), transfer of melanin to keratinocytes (1, 2, 3), response to inflammatory disease (1, 2), malignant transformation (4, 5, 6), chromosomal mutations (6, 7, 8), integrin expression (9), and *in vitro* response to pituitary hormones (1). Accordingly, one of ordinary skill in the art would understand that uveal melanocytes are so different from EM that the skilled artisan would have not reasonably expected an ingredient of a culture medium useful for culturing uveal melanocytes to be at all useful for culturing EM.

As a result, if at all motivated, one of ordinary skill in the art would be required to individually test the effect of any compound useful for culturing uveal melanocytes on EM cultures. Again, the standard for obvious is whether a person of ordinary skill in the art would have a reasonable expectation of success using the proposed combination of teachings, not whether it would have been obvious to try certain combinations. In light of the accepted evidence of dissimilarity between EM and uveal melanocytes, as provided in the literature and summarized in the enclosed Rule 132 Declaration, Applicants assert that there was no reasonable expectation of success of using hepatocyte growth factor to culture EM at the time of the present invention.

Accordingly, Applicants respectfully submit that neither Yanase, Swope nor HuII, taken singly or in combination, teach or suggest the presently claimed invention. As such, Applicants respectfully request that the rejections under 35 U.S.C. § 103(a) in view of the combination of Yanase, Swope and HuII be withdrawn.

CONCLUSION

Applicants believe that in light of the foregoing amendments and remarks, the claims are in condition for allowance, and accordingly, respectfully request withdrawal of the outstanding objections and rejections. An allowance is earnestly sought.

Respectfully submitted,

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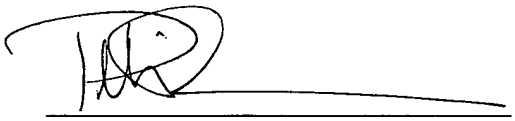

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